IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	))))	C.A. No. 05-356-KAJ (consolidated)

NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6)
TO PUREPAC PHARMACEUTICAL CO. AND ALPHARMA, INC.

PLEASE TAKE NOTICE that on April 11, 2006 commencing at 9:00 a.m., at the offices of Covington & Burling, 1201 Pennsylvania Avenue, N.W., Washington, D.C. 20004, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Plaintiffs" or "Janssen") will take the deposition upon oral examination of Defendants Purepac Pharmaceutical Co. and Alpharma, Inc. (collectively, "Purepac") pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure. This deposition upon oral examination will be conducted before an officer authorized to administer oaths and will be recorded by stenographic and videographic means.

Plaintiffs serve this Notice without waiver of its objections to the deficiencies in Purepac's document production and other discovery responses concerning the subject matter of the instant Notice, and reserve the right to continue this deposition as necessary in light of any subsequent document production by Purepac.

Plaintiffs will take this deposition upon oral examination through one or more officers, directors, managing agents or other persons designated by Purepac pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure as the person(s) knowledgeable to testify on Purepac's behalf concerning the topics identified in Schedule A. Purepac is requested to provide counsel for Plaintiffs with the identity of the individual(s) who will testify regarding

each topic at least one week in advance of the deposition. The deposition will continue from day to day until completed with such adjournments as to time and place as may be necessary. You are invited to attend and examine the witness(es).

ASHBY & GEDDES

/s/ Lauren E. Maguire

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Dated: February 21, 2006

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SCHEDULE A

Definitions

1. As used herein, "Purepac" shall mean Defendants Purepac Pharmaceutical Co. and Alpharma, Inc. and all of Purepac Pharmaceutical Co.'s corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees.

2. As used herein, "Purepac's ANDA" shall mean Purepac's Abbreviated New Drug Application Number 77-585.

3. As used herein, "the Generic Product" shall mean the proposed generic galantamine product that is the subject of Purepac's ANDA.

4. As used herein, "the '318 patent" shall mean United States Patent No. 4,663,318.

5. As used herein, "document" shall have the full meaning ascribed to it by the Federal Rules of Civil Procedure and shall include any means for retaining information.

6. As used herein, "FDA" shall mean the United States Food and Drug Administration.

7. As used herein, "Paragraph IV notice" refers to Purepac's April 29, 2005 letter to Plaintiffs attached hereto as Exhibit 1.

8. "Person" and "persons" mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

9. "Alzheimer's Disease" means any diagnosis, illness, or ailment described as being of the Alzheimer's type, including without limitation Senile Dementia of the Alzheimer's Type, and/or Alzheimer's Dementia.

10. "Galantamine" includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

Topics of Examination

1. Purepac's Paragraph IV notice including, without limitation, the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "claims 1 and 4 of the '318 patent, when properly interpreted, are invalid for a variety of reasons."

2. Purepac's Paragraph IV notice including, without limitation, the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "[a] summary of a talk given by P.A. Bhasker, M.D., D.M. entitled "Medical Management of Dementia" published in the journal *The Antiseptic*, Vol. 71, No. 1, pp 45-47 (January 1974)("Bhasker")(Ex.1) anticipates claim 1 of the '318 patent."

3. The circumstances under which Purepac first became aware of the P.A. Bhasker article cited in Purepac's Paragraph IV notice, *Medical Management of Dementia*, including how Purepac learned of it, who was involved in this first awareness, and any evaluation conducted of it by or on behalf of Purepac, then or subsequent to the time Purepac became aware of it.

4. Any evaluation, consideration or discussion conducted by Purepac to develop the Generic Product, including the names and responsibilities of all persons who were involved in the evaluation, consideration or discussion by Purepac to develop the Generic Product.

5. The decision to file an application with the FDA seeking approval to manufacture and sell a drug product containing galantamine.

6. Any evaluation, consideration or discussion conducted by Purepac to market the Generic Product, including the names and responsibilities of all persons who were

involved in the evaluation, consideration or discussion by Purepac to market the Generic Product.

7. The benefits, including revenues and profits, that Purepac projects, anticipates, expects, or forecasts it will obtain should Purepac's ANDA receive approval from the U.S. Food and Drug Administration.

8. Marketing strategies, marketing plans, and projected sales for Purepac's Generic Product.

9. Each and every contribution and/or input that Purepac, or any employee or agent of Purepac, has made to the preparation, decision to file, filing and/or prosecution of Purepac's ANDA, including: (a) any information relating to regulatory procedures and strategies for obtaining regulatory approval of the Generic Product of Purepac's ANDA; (b) any information comprising, relating to or contained in the 21 U.S.C. § 355(j)(2)(A)(vii)(IV) certifications submitted in connection with Purepac's ANDA; and (c) any information comprising, relating to or contained in the statements of factual and legal basis for invalidity, unenforceability, and/or noninfringement included with the notice of these certifications.

10. The factual basis for Purepac's proposed assertion that Purepac's ANDA is indicated for the treatment of mild to moderate Alzheimer's disease.

11. The circumstances in which Purepac first became aware of galantamine as a treatment for Alzheimer's disease, including but not limited to the date on which this occurred and the people involved.

12. The circumstances in which Purepac first became aware of the '318 patent, including but not limited to the date on which this occurred and the people involved.

13. Any consideration or evaluation by Purepac of developing a drug product containing galantamine for the treatment of Alzheimer's Disease.

14. Identification of all individuals, whether employees of Purepac or third parties, having a role in the consideration or evaluation by Purepac of developing a drug product containing galantamine for the treatment of Alzheimer's disease that is the subject of Topic 13, and a description of those roles.

15. Any effort by Purepac to develop any drug product other than the Generic Product set forth in Purepac's ANDA.

16. Identification of all individuals, whether employees of Purepac or third parties, having a role in the research, development or testing of such a treatment responsive to Topic 15, and a description of those roles.

17. The factual and legal bases for Purepac's Second Defense that each claim of the '318 patent is invalid for failure to satisfy one or more of sections 101, 102, 103, 112 and 116 of Title 35 of the United States Code.

18. The factual and legal bases for Purepac's Second Counterclaim that each claim of the '318 patent is invalid for failure to satisfy one or more of sections 101, 102, 103, 112 and 116 of Title 35 of the United States Code according to its proof elements, including an element-by-element comparison of each asserted claim of the '318 patent to the prior art Purepac relies upon and the motivation of one of skill in the art to combine any references under 35 U.S.C. §103, as well as a description of any non-prior art defenses such as lack of enablement, insufficient written description, failure to disclose best mode, or claim indefiniteness under 35 U.S.C. § 112.

19. The identity and location of documents and things concerning the foregoing topics.

20. Purepac's document retention policies from 1986 to the present.

21. Persons knowledgeable about the subject matter of the foregoing topics.

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EXHIBIT 1

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
Regulatory Affairs Department
One New England Avenue, Piscataway, New Jersey 08854
Telephone: 732-465-3632
Fax: 732-465-3791

April 29, 2005

Via Registered Mail
Return Receipt Requested

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutical, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Synaptech Inc.
c/o John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, NY 10023

Re: Galantamine Hydrobromide Tablets, Eq. 4 mg, 8 mg, and 12 mg Base
Paragraph IV Certifications for U.S. Pat. Nos. 4,663,318, 6,099,863 and 6,358,527

Dear Sirs:

Purepac Pharmaceutical Co. ("Purepac"), a subsidiary of Alpharma, Inc., is providing the following information pursuant to § 505(j)(2)(B)(ii) of the Federal Food, Drug, and Cosmetic Act ("the Act"):

1. In order to obtain approval to engage in the commercial manufacture, use, or sale of certain galantamine[1] hydrobromide formulations ("the PROPOSED PRODUCTS"), Purepac submitted to the Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Act that contains the required bioavailability or bioequivalence data or information. The FDA has documented the receipt of this application and has notified Purepac accordingly.

2. The ANDA number is 77-585.

3. The established names for the PROPOSED PRODUCTS are galantamine hydrobromide tablets, eq. 4 mg, 8 mg, and 12 mg base. Janssen markets galantamine hydrobromide tablets, eq. 4 mg, 8 mg, and 12 mg base under the brand name Razadyne® (formerly known as "Reminyl®").

[1] "Galantamine" is also referred to as "galanthamine."

4. The active ingredient, strength, and dosage form of the proposed drug product is galantamine hydrobromide tablets, eq. 4 mg, 8 mg, and 12 mg base.

5. The ANDA indicates that Purepac intends to market the PROPOSED PRODUCTS before the expiration date of U.S. Patent Nos. 4,663,318 ("the '318 patent"), 6,099,863 ("the '863 patent), and 6,358,527 ("the '527 patent"). These patents were listed by the FDA in the Orange Book.

6. The ANDA indicates that the claims of the '318 patent, the '863 patent, and the '527 patent are invalid and/or will not be infringed by the commercial manufacture, use, or sale of the PROPOSED PRODUCTS. Below is a detailed statement of the factual and legal bases for Purepac's conclusions. This information is supplied for the sole purpose of complying with the above-referenced statutes. Accordingly, Purepac does not waive any attorney-client privilege or work product immunity concerning the subject matter of this communication.

I. Relevant Law

A. Law Regarding Claim Construction

Claims are always in the form of a single sentence, usually having a preamble and one or more "elements" or "limitations". The limitations of the claims provide the measure for patentability, as well as infringement. To analyze either the validity or infringement of a patent, therefore, the patent claims must first be construed to determine their proper scope and content. *See, e.g., Minnesota Mining and Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed. Cir. 1992). A patent construction, including terms of art within its claim, is exclusively within the province of a judge. *Markman v. Westview Instruments, Inc.*, 116 S.Ct. 1384, 38 U.S.P.Q.2d 1461 (1996), *affirming* 52 F.3d 967, 34 U.S.P.Q.2d 1321 (Fed. Cir.) (*en banc*).

Terms in a patent claim can be defined only in a way that comports with the patent as a whole. *Markman*, 116 S. Ct. at 1395. All claim analyses begin and end with a focus on the claim language itself. *Thermalloy, Inc. v. Aavid Eng'g, Inc.*, 121 F.3d 691, 693 (Fed. Cir. 1997) (stating that "throughout the interpretation process, the focus remains on the meaning of the claim language."). Proper construction of a patent claim requires consideration of all the sources of meaning of the claim in the PTO record, namely the claim language itself, the written description, and the prosecution history including the cited prior art. *Markman*, 52 F.3d at 979; *Amhil Enterprises Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1559-62 (Fed. Cir. 1996). Where a claim term is unambiguous in light of the specification and file history, there is no need to resort to extrinsic evidence. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 39 U.S.P.Q. 1573 (Fed. Cir. 1996). However,

> extrinsic evidence is to be used in the court's understanding of the patent .... such evidence [is considered to be] an aid to the court in coming to the correct conclusion as to the true meaning of the language employed in the patent.

Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 46 U.S.P.Q.2d 1169 (Fed. Cir. 1998) (*en banc*). The court is free to consult a dictionary at anytime. *Id.*

B. Law Regarding Validity – Anticipation And Obviousness

A claim is anticipated, and therefore invalid under 35 U.S.C. § 102, if each claimed element is found in a single prior art reference. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991); *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 138 (Fed. Cir. 1986). There must be no difference between the claimed invention and the reference disclosure, as viewed by an ordinary artisan. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d at 1576.

If a patent is attacked for lack of novelty, or as being obvious, the presumption of validity is more easily overcome by the challenger's showing of more material prior art than that considered by the PTO. *Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 885 (Fed. Cir. 1984); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983).

Patentability is precluded if the subject matter as a whole would have been obvious to an ordinary artisan at the time the invention was made. 35 U.S.C. § 103. Obviousness is a conclusion of law based on a number of underlying factual inquiries. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1572 (Fed. Cir. 1988). The Supreme Court has stated that three factual determinations are required in an analysis under §103: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Secondary considerations bearing on obviousness must also be considered. *Id. at* 17-18; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d at 1538.

C. Law Regarding Infringement – Literal And Under The Doctrine Of Equivalents

Courts analyze infringement in two steps. First, the court construes the patent claims asserted to be infringed as a matter of law. The second step is comparing the properly construed claims to the device or method accused of infringing. *Markman v. Westview Instruments Inc.*, 52 F.3d 967, 34 U.S.P.Q.2d 1321 (Fed. Cir. 1995) (*en banc*), *aff'd*, 116 S.Ct. 1384, 38 U.S.P.Q.2d 1461 (1996).

To establish literal infringement, every limitation set forth in a claim must be found in an accused product. *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 117 S.Ct. 1040, 41 U.S.P.Q.2d 1865 (1997), *on remand*, 114 F.3d 1161, 43 U.S.P.Q.2d 1152 (Fed. Cir. 1997). "If even one limitation is missing or not met as claimed, there is no literal infringement." *Mas Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).

Further, in the absence of infringement of the independent claims, there can be no infringement of dependent claims. "One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all of the limitations of) that claim." *Eltech Systems v. PPG Industries*, 710 F. Supp. 622, 634 n.10; 11 U.S.P.Q.2d 1174, 1184 n.10 (W.D. La. 1988), *aff'd*, 903 F.2d 805, 14 U.S.P.Q.2d 1965 (Fed. Cir. 1990).

Even where no literal infringement exists, a device may infringe a patent under the doctrine of equivalents. *Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co.*, 339 U.S. 605, 613 (1950). The doctrine of equivalents permits courts to extend the scope of protection beyond the claim's literal meaning. However, broad application of the doctrine of equivalents conflicts with the statutory requirement that the claims define the invention. *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 117 S. Ct. 1040, 1049 (1997). The Supreme Court in *Warner-Jenkinson* refused to adopt a particular linguistic framework for analyzing infringement under the doctrine of equivalents. *Warner-Jenkinson*, 117 S. Ct. at 1054. Instead, the Supreme Court stated that the "essential inquiry" was:

> Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention? Different linguistic frameworks may be more suitable to different cases, depending on their particular facts. A focus on individual elements and a special vigilance against allowing the concept of equivalence to eliminate completely any such elements should reduce considerably the imprecision of whatever language is used. An analysis of the role played by each element in the context of the specific patent claim will thus inform the inquiry as to whether a substitute element matches the function, way, and result of the claimed element, or whether the substitute element plays a role substantially different from the claimed element.... We expect that the Federal Circuit will refine the formulation of the test for equivalence in the orderly course of case-by case determinations, and we leave such refinement to that court's sound judgment in this area of its special expertise.

Id. at 1054.

The Court of Appeals for the Federal Circuit has made it clear that the doctrine of equivalents is not intended to be used as a general mechanism for a patentee to expand the scope of a patent's claims. Significant limitations have been placed on the application of the doctrine. First, to infringe under the doctrine of equivalents, a product must include each and every element of a claim or its equivalent. *Warner-Jenkinson*, 117 S. Ct. at 1049 (stating that "[i]t is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety."). "[T]he doctrine of equivalents is not a license to ignore or erase ... structural and functional limitations of the claim, limitations on which the public is entitled to rely in avoiding infringement." *Athletic Alternatives, Inc. v. Prince Manu., Inc.*, 73 F.3d 1573, 1582 (Fed. Cir. 1996) (internal quotations omitted).

II. The Claims Of The '318 Patent Are Invalid And/Or Not Infringed

For at least the reasons discussed below, the claims of the '318 patent are invalid and/or not infringed.

A. The '318 Patent

The '318 patent is generally directed to a method of treating Alzheimer's disease and related dementias by administering galantamine or a pharmaceutically-acceptable acid

addition salt thereof to a patient in need. The '318 patent issued with seven claims directed to the treatment of Alzheimer's disease and other dementias by the administration of galantamine. The only independent claim, claim 1, is reproduced below:

> 1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

Dependent claims 2-3 are directed to the parenteral delivery of galanthamine or salt thereof at a daily dosage of 5-1,000 milligrams per day and 50-300 milligrams per day, respectively.

Dependent claims 4-5 are directed to the oral administration of galanthamine salt thereof at a daily dosage of 10-2,000 milligrams per day and 100-600 milligrams per day, respectively.

Dependent claim 6 is directed to the parenteral administration of galanthamine at a dosage rate of 0.1 to 4 milligrams/kilograms (mg/kg) body weight of a patient. Finally, claim 7 is directed to the administration of galanthamine intracerebroventricularly via an implanted reservoir.

B. Invalidity Analysis

Claims 1 and 4 of the '318 patent, when properly interpreted, are invalid for a variety of reasons.

1. Claim 1 Of The '318 Patent Is Anticipated By The Prior Art

A summary of a talk given by P.A. Bhasker, M.D., D.M. entitled "Medical Management of Dementia" published in the journal *The Antiseptic*, Vol. 71, No. 1, pp. 45-47 (January 1974) ("Bhasker") (Ex. 1) anticipates claim 1 of the '318 patent under 35 U.S.C. § 102(b).

The Bhasker reference links use of cholinesterase inhibitors such as galantamine with improving higher cortical functions in patients suffering from dementia in an article directed generally to medical management of progressive dementias. Bhasker was not before the Examiner when the application that resulted in the '318 patent was being examined. Bhasker is more pertinent than the art before the examiner, as it specifically teaches use of galantamine for the medical management of progressive dementia.

Because each and every limitation of claim 1 is disclosed in Bhasker, claim 1 of the '318 patent is invalid for lack of novelty under 35 U.S.C. § 102(b).

2. Claims 1 And 4 Of The '318 Patent Are Obvious Over the Prior Art

At least the following combinations of references render claims 1 and 4 of the '318 patent obvious.

(a) **Claim 1 Is Obvious In View Of Bhasker Or GB 0 942 200 In View Of Smith Or Davis**

Claim 1 is obvious over the Bhasker reference or GB 0 924 200 in view of either of two publications. The first publication is "Physostigmine in Alzheimer's Disease" in *The Lancet*, p. 42, January 6, 1979 ("Smith") (Ex. 2). The second publication is *Am. J. Psychiatry*, Vol. 139, pp. 1421-1424 (1982) ("Davis") (Ex. 3).

During prosecution of the application leading to the '318 patent, the patentee alleged that prior art teaching merely that galantamine enhanced short-term memory did not indicate that the compound would be useful to treat Alzheimer's disease and related dementias.

Nothing before the Examiner, however, linked galantamine directly with the treatment of progressive dementias or Alzheimer's disease. Bhasker provides this link, as does GB '200. In an article discussing medical management of dementias, including progressive dementias, Bhasker suggests the use of cholinesterase inhibitors such as galantamine to restore higher cortical function. GB '200 discloses that galantamine hydrobromide is a strong cholinesterase inhibitor having an activity similar to that of eserine (physostigmine). Both Smith and Davis disclose use of the cholinesterase inhibitor physostigmine to treat Alzheimer's disease. These references are therefore more pertinent than the references before the examiner, because they provide a direct link between galantamine and use of galantamine to treat Alzheimer's disease and related dementias.

As of 1982, there was general knowledge in the art that cholinesterase inhibitors could be used to treat progressive dementias, including Alzheimer's disease. Davis suggested that a cholinergic deficit contributes to the cognitive changes in Alzheimer's patients and treatment of the disease may be accomplished by a reversal of the cholinergic deficit, which can be effected by the administration of the anticholinesterase physostigmine. (Ex. 3, page 1423) Smith also indicated that dosing Alzheimer's patients with an anticholinesterase compound, specifically physostigmine, could be used to improve memory in patients suffering from the disease. Finally, Bhasker disclosed work showing that higher cortical functions in patients suffering from dementia could be restored by the "facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors" such as galantamine. (Ex. 1, page 46) These references provide the motivation to use galantamine to treat Alzheimer's disease and related dementias.

In addition, because Smith and Davis reference anticholinesterase physostigmine in the successful treatment of Alzheimer's patients, and because it was known from GB'200 that galantamine hydrobromide is a strong anticholinesterase having an activity similar to that of physostigmine, it would have been obvious to one of ordinary skill in the art to treat patients suffering from Alzheimer's disease with galantamine.

In sum, the use of galantamine to treat Alzheimer's would have been obvious to one of ordinary skill in the art based on prior art that was not before the Examiner during prosecution of the claims of the '318 patent. Accordingly, claim 1 of the '318 patent is invalid as obvious over Bhasker and/or GB '200 in view of Smith and/or Davis.

(b) **Claim 4 Is Obvious In View Of: Bhasker, The '975 Application, And The GB '200**

Claim 4 depends from claim 1 and further requires the administration to be oral and the amount of galanthamine or pharmaceutically acceptable acid addition salt to be in the range of 10-2000 milligrams per day. Claim 4 of the '318 patent is rendered obvious for the reasons described above, further in view of EP 0 098 975A1.

Bhasker discloses use of "small daily doses" of galantamine (Exh. 1, page 46), and GB '200 discloses 0.25-10 mg galantamine hydrobromide per day. EP '975 discloses use of oral dosage capsules containing 5 mg of galanthamine hydrobromide. One of ordinary skill in the art would have been motivated to use the oral dosage capsule of EP '975 to provide the "small daily dosage of galanthamine" of Bhasker, for example the 0.25 to 10 milligrams of GB '200.

The oral daily dosage form of 10-2000 milligrams per day would thus have been obvious in view of this prior art, since an overlap of even a single endpoint can be enough to establish a *prima facie* case of obviousness. *See, e.g., In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90, 104 (C.C.P.A. 1976); *In re Woodruff*, 919 F.2d 1575, 16 U.S.P.Q.2d 1934 (Fed. Cir. 1990) (holding that the term "about 1-5%" carbon monoxide taught by prior art overlapped with a claim limitation of "more than 5%" carbon monoxide.) Here, Claim 4 of the '318 patent requires the oral administration of galantamine or a salt thereof in the range 10-2000 milligrams per day. EP '975 discloses oral dosage forms comprising 5 milligrams of galantamine hydrobromide per capsule. GB '200 discloses that galantamine hydrobromide can be delivered in amounts of 0.25-10 milligrams per day. The overlap in the claimed range with the range found in GB '200 therefore establishes *prima facie* obviousness.

Accordingly, claim 4 of the '318 patent would have been obvious to one of ordinary skill in the art based on prior art that was not before the Examiner during prosecution of the patent.

C. Infringement Analysis

The PROPOSED PRODUCTS would not infringe at least claims 2-3 and 5-7 of the '318 patent literally or under the doctrine of equivalents.

1. Literal Infringement

Claims 2-3 and 6-7 of the '318 patent are directed to treating a patient by the parenteral or intracerebroventricular administration of galantamine or a pharmaceutically acceptable salt thereof. The PROPOSED PRODUCTS will be solid dosage forms for oral administration. The solid dosage form cannot be administered parenterally or intracerebroventricularly, as these modes of administration require the active agent to be in liquid form, e.g., solution or suspension. Therefore, use of the PROPOSED PRODUCTS would not directly infringe claims 2-3 and 6-7 of the '318 patent as the dosage forms would not meet at least one limitation of these claims.

Claim 5 is directed to treating a patient by oral administration of galantamine or a pharmaceutically acceptable salt thereof at a dosage rate of 100-600 milligrams per day. As a threshold matter, since the dosage range of claim 5 is outside the range for which FDA approval has been granted, Janssen may not bring a claim for infringement of claim 5 under 35 U.S.C. Section 271(e)(2). *See Allergan, Inc. v. Alcon Laboratories, Inc.*, 324 F.3d 1322, 1333-34 (Fed. Cir. 2003) (" a method of use patent holder may not bring an action under Section 271(e)(2) for infringement of a method of use patent that does not claim a FDA-approved use.") *citing Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

Further, even if a claim for infringement under Section 271(e)(2) were somehow proper, the PROPOSED PRODUCTS will be provided with instructions recommending that the galantamine hydrobromide tablets are to be dosed at 16-24 milligrams per day, since a 32 milligram per day dose is less well tolerated than lower doses, and does not provide increased effectiveness. Use of the tablets in accordance with the dosage instructions would therefore not directly infringe claim 5 of the '318 patent as this use of the PROPOSED PRODUCTS would not satisfy at least one limitation of claim 5 of the '318 patent, i.e., a dosage rate of 100-600 milligrams per day.

2. Infringement Under The Doctrine Of Equivalents

Here, the PROPOSED PRODUCTS are solid dosage forms to be administered orally. In contrast, claims 2-3 and 6-7 require the parenteral or intracerebroventricular administration of galantamine or a pharmaceutically-acceptable salt thereof. Use of the PROPOSED PRODUCTS via oral administration would not infringe claims 2-3 and 6-7 of the '318 patent under the doctrine of equivalents because oral administration does not meet at least the "way" prong of the function/way/result test. Oral administration requires the ingestion by the patient of the drug and subsequent absorption into the system through the digestive tract. Parenteral administration, on the other hand, is by intravenous, intramuscular, or subcutaneous injection. Cerebroventricular administration is even more localized to the brain as the galantamine or a pharmaceutically-acceptable salt thereof is administered "via an implanted reservoir" (claim 7).

Therefore, use of the PROPOSED PRODUCTS would not infringe claims 2-3 and 6-7 of the '318 patent, as oral administration of galantamine hydrobromide would not function in at least substantially the same way as parenteral or cerebroventricular administration.

Use of the PROPOSED PRODUCTS in accordance with the provided instructions would not infringe claim 5 of the '318 patent under the doctrine of equivalents, because the dosage amounts per day would be significantly less than 100-600 milligrams per day as is required by claim 5.

Here, there is more than an insubstantial difference between the claimed dosage rate of 100-600 milligrams per day and the dosage instructions for the PROPOSED PRODUCTS. The dosage instructions will recommend that the daily dose of galantamine hydrobromide be in the range of 16-24 milligrams. This is four times less than the minimum amount required by the claim. A conclusion that the 16-24 milligram formulation would infringe a claim requiring 100-600 milligrams would eviscerate the plain meaning of the limitation.

Accordingly, use of the PROPOSED PRODUCTS in accordance with the label instructions would not infringe claim 5 of the '318 patent under the doctrine of equivalents.

III. The Claims Of The '863 And '527 Patents Are Not Infringed

For at least the reasons discussed below, the claims of the '863 and '527 patents are not infringed.

A. The '863 and '527 Patents

The '863 patent and the '527 patent are generally directed to galantamine hydrobromide tablets, in particular tablets containing a diluent that is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25).

1. The '863 Patent

The '863 patent issued with 10 claims, including one independent claim reproduced below:

> 1. A tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.

(Emphasis added) Dependent claim 2 further limits the disintegrant to crospolyvidone or croscarmellose. Claims 3 and 4 add a glidant and a lubricant.

Dependent claims 5 and 6 further limit the amount of each component in the tablet.

Dependent claims 7-9 are directed to film-coated tablets. Finally, claim 10 is directed to a process of preparing a tablet according to claim 3.

2. The '527 Patent

The '527 patent issued with 6 claims, including two independent claims, claims 1 and 6. Claim 1 is reproduced below.

> 1. A method of treating a disorder selected from dementia, mania or nicotine dependence in a patient in need thereof comprising administering to the patient a tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.

(Emphasis added) Dependent claims 2, 3, 4, and 5 further limit the disorders to dementia, Alzheimer's dementia, mania, and nicotine dependence.

Claim 6 is reproduced below:

> 6. A fast-dissolving galanthamine hydrobromide (1:1) tablet made by (i) dry blending the active ingredient, an insoluble or poorly soluble cross-linked polymer disintegrant and an optional glidant with a diluent comprising a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25); (ii) optionally mixing a lubricant with the mixture obtained in step (i); (iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and (iv) optionally film-coating the tablet obtained in step (iii).

(Emphasis added)

B. Infringement Analysis

None of the PROPOSED PRODUCTS would infringe the claims of the '863 and '527 patents literally or under the doctrine of equivalents.

1. Literal Infringement

None of the PROPOSED PRODUCTS would literally infringe the claims of the '863 or '527 patents. This analysis will focus on the three independent claims of the two patents, since, should it be found that none of the PROPOSED PRODUCTS infringe the independent claims, they would not infringe any of the claims which are dependent upon the independent claims.

Claim 1 of the '863 patent requires a tablet comprising a *carrier* wherein the carrier comprises, *inter alia*, a diluent that is *a spray-dried mixture of lactose monohydrate and microcrystalline cellulose* (75:25). Claim 1 of the '527 patent requires a method comprising administering a tablet comprising a *carrier* wherein the carrier comprises, *inter alia*, a diluent that is *a spray-dried mixture of lactose monohydrate and microcrystalline cellulose* (75:25). Claim 6 of the '527 patent requires a tablet comprising, *inter alia*, a diluent that is *a spray-dried mixture of lactose monohydrate and microcrystalline cellulose* (75:25). None of the components used to prepare the tablet core (or the film coating) of the PROPOSED PRODUCTS will contain microcrystalline cellulose, let alone *a spray-dried mixture of lactose monohydrate and microcrystalline cellulose in a ratio of 75:25*. Therefore, the PROPOSED PRODUCTS and their use would not literally infringe claim 1 of the '863 patent, nor would they infringe claim 1 or claim 6 of the '527 patent, as they would not satisfy at least these limitations in the claims. Because there would be no infringement of claim 1 of the '863 patent, there would also be no infringement of claims 2-10 of the '863 patent, which depend from claim 1 of the '863 patent. There would also be no infringement of claims 2-5 of the '527 patent, which depend from claim 1 of the '527 patent.

2. Infringement Under The Doctrine Of Equivalents

The PROPOSED PRODUCTS would not infringe the '863 or '527 patent claims under the doctrine of equivalents at least because none of the elements of the accused products

functions in substantially the same way as limitations in the claims requiring a *carrier* or diluent comprising a spray-dried mixture comprising *microcrystalline cellulose*. The components of the claimed carrier and the components of the PROPOSED PRODUCTS function in a different way, since the components of the PROPOSED PRODUCTS have different chemical and physical properties in comparison to microcrystalline cellulose. In fact, this claim element is entirely missing in the PROPOSED PRODUCTS, which do not contain microcrystalline cellulose. Accordingly, any claim of infringement under the doctrine of equivalents is precluded as a matter of law. *Warner-Jenkinson*, 117 S. Ct. at 1054.

IV. Conclusion

For at least the reasons stated above, the claims of the '318, '863, and '527 patents are invalid and/or not infringed. As such, the '318, '863, and '527 patents do not prohibit Purepac from marketing PROPOSED PRODUCTS, as defined by ANDA No. 77-585, once the FDA approves Purepac's ANDA.

Very Truly Yours,

Ken Smith /TN

Ken Smith
Vice President, Chief Patent Counsel
Alpharma, Inc.

EXHIBIT 1

MEDICAL MANAGEMENT OF DEMENTIA*

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Dementia is neither a disease per se nor a single symptom. It may be considered to be a clinical manifestation resulting from complex structural or functional changes in the more sophisticated mechanisms of the brain. The corrective treatment is usually therefore, one associated with a gloomy outlook, because a dementing process in most cases is a relentlessly progressive one, and very often not amenable even to diagnosis.

On the other hand, this gloomy picture is thoroughly wiped out and a favourable result readily obtained when one of the treatable underlying causes is detected; the prognosis becomes excellent when the correctable cause is diagnosed early and found to be a metabolic or endocrine deficit (as in Pellagra, B12 deficiency or Myxoedema). In such cases, the dementia can be cleared up and the patient can have a complete "cure".

On the other hand, the dementing process can be arrested or reversed to a minor extent in some instances, where only a guarded prognosis can be offered. These situations include the cases of tumours (when removable), infections (like GPI) when they can be "successfully" arrested, post-traumatic dementias, and low pressure hydrocephalus.

The irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill. Therefore, the importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care. Moreover it must be emphasised that in certain situations (like Myxoedema) a *late* diagnosis of the underlying cause may lead to irreversibility of the mental status, especially so, in the young developing brains.

With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible. The problem of who is going to manage the dementing individual arises next. Contrary to the older beliefs that the demented person (who is likely to be insane) has to be necessarily managed by a psychiatrist or an internist, it now appears that the Neurologist is the best person to handle them, and a neuropsychiatrist is the ideal person. The neurologist remains today at the centre of a triangle formed by the psychiatrist, the general physician and the neurosurgeon.

*Summarized from the talk given to the Institute of Neurology. Specially contributed to the 'Anvilnarie'.

The control of convulsions and involuntary movements are separate subjects by themselves. But what must be stressed is the importance of controlling these associated disorders which may sometimes assume greater importance than the dementia itself. For example, in cases of Huntington's chorea, where the dementia may be very slowly progressive, the involuntary movements may present the main problem, when adequate control of the choreic movements enables the individual to go back to his work. Rewarding experiences are on record of having treated patients with Huntington's Chorea by giving Haloperidol, a very useful drug in the control of hyperkinetic dyskinesias.

The behavioural problems met with in patients with dementia are profound and so depending upon the nature of the behavioural disturbance, judicious use may be made of drugs, along with psychiatric care. General surgical therapy does not find a significant role in dealing with patients suffering from progressive dementia except when there is an isolated behavioural aberration that can be selectively tackled by Stereotaxy. Even then, any beneficial response is short-lived and soon overtaken by the demenring process.

A demented person obviously requires careful supervision and devoted nursing care as he will not be able by himself to attend to his own nutrition and personal cleanliness; he is also likely to be unmindful of any intercurrent illnesses that may supervene.

The restoration of higher cortical functions is difficult and was once considered to impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). Empirical measures, like trying anabolic steroids, vasodilators, nucleic acid preparations, amines and aminoacids are in vogue, but have not been of any great value. The problem of sending a demented individual back to his profession has to be adequately studied by the attending physician before coming to a definite decision. If he happens to hold a position requiring the use of proper judgement, it is better that he is relieved of such a responsible post and assigned a less exacting, general type of work.

The social aspects include adequate counselling in marriage affairs when a demented person or a relative of a demented

person seeks advice. The stigma associated with dementia is equal to that with epilepsy. This fact must be kept in mind by the physician, when confronted with a case of dementia and especially the relatives.

The problem of managing a demented individual is a very real one needing adequate judgement, judicious use of drugs, sympathetic nursing and proper counselling.

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DEATHS INVOLVING PROPOXYPHENE

A STUDY OF 41 CASES OVER A TWO-YEAR PERIOD

Forty-one deaths occurred involving propoxyphene hydrochloride (Darvon) during a two year period. Ten patients died from propoxyphene intoxication alone, while 12 were victims of a propoxyphene alcohol combination, the latter number being identical to the deaths from a combination of barbiturates with alcohol seen during the same period. Five young women died from an ingestion of propoxyphene following an argument. Four patients could be categorized as drug abusers due to historical circumstances. The high levels of propoxyphene suggested habituation in three instances. Physicians should be alerted to the potential deleterious effects of indiscriminate use and abuse of propoxyphene, and should warn their patients not to drink alcoholic beverages when taking propoxyphene. They should use extreme caution when prescribing it to those in the younger age group.

An impressive factor in this series is the availability of the drug to young people who, after a sudden argument, seem to find ingestion of pills a convenient gesture at attempted self-destruction. There were five cases of teenagers (all girls) in this series (aged 15 to 20 years) whose deaths were caused by propoxyphene intoxication, and in none of these were alcohol, other drugs or narcotics addiction involved. In two instances, the victims were found to be pregnant. Ten of the 22 patients who died from ingestion of propoxyphene alone, or propoxyphene in combination with alcohol, were over 40 years of age, while two of the deaths due to the combination were in patients over 60 years of age.

Concerning the manner of death, 17 of the 41 cases were classified as suicide, with six of these solely from the ingestion of propoxyphene.

Eighteen of the 41 patients received a prescription of propoxyphene from one or more private physicians. Seven of these patients eventually died from ingestion of propoxyphene or propoxyphene with alcohol. In 12 instances, the patient secured a prescription as an outpatient from a clinic. —[Sturner Q. William and Garriott C. James, *J.A.M.A.*, 5-3-1973].

EXHIBIT 2

PHYSOSTIGMINE IN ALZHEIMER'S DISEASE

SIR,—Impairment of presynaptic cholinergic neurotransmission may cause the characteristic short-term memory disorder found in the early stages of Alzheimer's disease.[1] Cholinergic drugs might therefore improve memory in this disorder. We have studied the effects of the anticholinesterase drug physostigmine on memory and intellectual capacity in a patient with familial Alzheimer's disease. The diagnosis was confirmed by right frontal-lobe biopsy. The patient was a 42-year-old man, whose mother and uncle had died of dementia before the age of 55. Progressive memory loss and personality change had occurred during the previous 2 years, and he was moderately demented. Speech was fairly fluent but there were some paraphasic substitutions. Informed consent for the drug was given, both by the patient and by his wife.

During a 3-week practice period the patient was tested six times so that he became familiar with the tests. A standard set of instructions was devised which he could understand. After this, in a double-blind study, physostigmine salicylate, 1 mg subcutaneously, or a saline placebo injection, were allocated randomly in the blocks of two. Testing was always done at the same time of day, and sessions were spread over a 7-week period. Testing started 15 min after the injection, and was completed within an hour. Tests were selected or devised to suit the residual abilities of the patient. A non-verbal test of intellectual capacity (Raven's progressive coloured matrices[2]) was used. The remainder were memory tests. In immediate verbal memory tests, recall of word lists which had just been read out to him was tested (high-frequency words from the Thorndike and Lorge[3] AA list were used). With successive lists, free recall, recall with the help of category cues, and the ability to recognise when they were mixed with distractors [illegible] were tested. Drawings of common objects were used in a visual recognition test. To test memory for material already in store, the patient was asked to recall as many boys' names as he could in one minute. Memory after delay and distraction was tested using more meaningful material (name, address, "shopping-list", photographs of faces) presented at the beginning of the session; memory for this material was tested after completion of the other tests.

As shown in the table, not only was memory for verbal material poor, especially after delay and distraction, but also a large number of inappropriate responses or intrusions occurred. Physostigmine did not affect the number of correct responses but reduced the number of inappropriate responses on the free-recall word-list ($p=0.052$), the cued-recall word-list ($p=0.026$) and recall of boys' names ($p=0.034$). Performance on the other tests was not significantly affected by physostigmine. It would appear that the reduction in intrusion errors was not simply a non-specific depressant effect of the drug since the number of correct responses was not significantly reduced by physostigmine on any of the tests. We have consistently observed a high incidence of intrusion errors in patients with Alzheimer's disease—indeed these patients make a higher proportion of intrusion errors than do age-matched controls.[4] The memory disorder is not simply a problem of establishing new material in store since Miller[5] has shown that in certain cued-recall tests patients with Alzheimer's disease perform as well as controls. In our patient, efficient storage of information was demonstrated by the free-recall word list test in which 85% of the patient's errors consisted of words given in previous ten sessions. It has been suggested that the inability to inhibit the recall of irrelevant information may contribute to the memory disorder in Alzheimer's disease.[6]

The brain biopsy tissue was examined by Dr D. Bowen's group at the Institute of Neurology. The choline acetyltransferase content was only 25% of that found in control brains (see fig. 1 in the paper by Bowen et al. on p. 11 of this issue).

The reduction in intrusion errors observed after physostigmine in this patient, whose Alzheimer's disease was fairly advanced, indicates that further studies using carefully controlled test procedures, designed to test patients' individual disabilities at an earlier stage of their disease are worthwhile.

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RESULTS OF MINOR TESTS: MEAN±S.E.M.

Test	Score: Max. possible	After placebo	After physostigmine	P*
Raven's progressive matrices	60	11·0±0·63	11·67±0·56	n.s.
Immediate memory: verbal				
Free recall				
Correct	60	8·00±1·26	7·17±0·80	n.s.
Intrusions		5·00±1·26	1·33±0·42	0·052
Category-cued recall				
Correct	12	1·0±0·63	1·5 ±0·34	n.s.
Intrusions		10·0±1·34	4·3 ±1·56	0·026
Recognition	6	3·17±0·31	3·00	
Immediate memory: visual				
Object recognition	2	1·67±0·21	1·57±0·21	n.s.
Memory for boys' names:				
Correct		6·83±0·31	7·57±0·56	n.s.
Intrusions		2·83±0·31	1·33±0·42	0·03
Memory after delay				
Name, address, Shopping lists	6	..	..	
Correct	6	1·33±0·42	0·67±0·42	n.s.
Intrusions		4·33±0·56	2·50±0·67	n.s.
Photographs	4	3·17±0·17	3·00±0·36	n.s.

*Mann-Whitney *U* test, two-tailed. n.s.=not significant.

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2. Raven, J. C. Guide to Using the Coloured Progressive Matrices. Sets A, Ab, B. London, 1965.
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COT DEATHS AND WATER SODIUM

SIR,—Dr Robertson and Dr Parker (Nov. 11, p. 1012) have cited the changes in the sodium content of the water supply in Scunthorpe as significantly affecting the incidence of cot deaths in that area. Their findings prompt me to review data which I collected over the decades 1950–59 and 1960–69 in Hartlepool.

The post-neonatal mortality-rate in Hartlepool declined from 14·4 in the decade 1950–59 to 8·6 per 1000 live births in 1960–69. The fall took place during a period of improved hospital and specialist services and also during a period of falling incidence of prematurity. The incidence of sudden-infant-death syndrome (s.i.d.s.) in infants aged 1–12 months fell from 3·63 per 1000 live births in 1950–59 to 3·00 per 1000 in 1960–69, but this fall was not statistically significant.

s.i.d.s. has been defined[1] as "the sudden death of any infant or young child which is unexplained by history and in which a thorough post mortem examination fails to demonstrate an adequate cause of death". In my study[2] s.i.d.s. was diagnosed by exclusion, but the pathological findings in cases recorded as s.i.d.s. were identical with cases reported elsewhere in the

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2. Milligan, R. C. *Publ. Hlth. Lond.* 1974, 88, 69.

EXHIBIT 3

Am J Psychiatry 139:11, November 1982

REGULAR ARTICLES

Enhancement of Memory Processes in Alzheimer's Disease with Multiple-Dose Intravenous Physostigmine

BY KENNETH L. DAVIS, M.D., AND RICHARD C. MOHS, PH.D.

Physostigmine (.125 mg, .25 mg, or .50 mg) or placebo was administered intravenously to 10 neuroleptic-free patients with Alzheimer's disease over a 30-minute period. All patients performed better on a recognition memory task while receiving physostigmine. When placebo or the dose of physostigmine previously associated with an improvement in memory was readministered, physostigmine again enhanced performance on a recognition memory task. These results indicate that the acute augmentation of cholinergic activity in some patients with Alzheimer's disease can partially reverse the memory deficit of that disorder and may provide an approach to the eventual therapy of this condition. (Am J Psychiatry 139:1421-1424, 1982)

Recent studies have demonstrated that Alzheimer's disease, the most common cause of dementia among elderly people, is a disorder that impairs the functioning of cholinergic neurons. Patients with Alzheimer's disease have a dramatic loss of brain choline acetyltransferase (1–10), a marker for intact cholinergic neurons (11). The loss of brain choline acetyltransferase activity has been correlated with both the degree of dementia and the histopathological changes in the brain that are characteristic of Alzheimer's disease (8). On the basis of these findings and the fact that choline and phosphatidylcholine, precursors of acetylcholine, can increase acetylcholine concentrations in the brain (12–16), many studies have been conducted to investigate the effects of these precursors on memory in normal people and patients with Alzheimer's disease (17–28). Unfortunately, these studies have not convincingly demonstrated any reliable enhancement of memory after treatment with precursors of acetylcholine. Alternative methods for pharmacologically enhancing cholinergic activity include the use of cholinesterase inhibitors and cholinergic agonists. Both physostigmine, a short-acting cholinesterase inhibitor, and arecoline, a short-acting cholinergic agonist, have been shown to enhance storage of information into memory when given in low doses to healthy young adults (29, 30). We are now able to report that physostigmine also acutely enhanced memory when given, under double-blind conditions, to 10 patients with Alzheimer's disease.

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METHOD

The sample consisted of 8 male and 2 female patients between the ages of 50 and 68 years. The diagnosis of Alzheimer's disease was made with the aid of computerized tomographic scan, brain skull films, CSF analysis, serum analysis, a carefully taken history, and physical examination. Particular care was given to ruling out cases of multi-infarct dementia. All patients had a Memory and Information Test score of 10 or less and/or a Dementia Rating Scale score of 4 or more. These criteria have been shown to identify patients with a high probability of Alzheimer's disease, as verified by histopathological examination on autopsy (31). The patients had been free of all psychoactive agents for at least 2 weeks before physostigmine administration, with the exception of an occasional dose of chloral hydrate at bedtime. The patients were not psychotic or agitated and were able to cooperate with the cognitive testing procedures. In practice, the 2 previously mentioned criteria defined a rather homogeneous group of moderately demented but cooperative subjects.

Because of the unusual dose-response characteristics of physostigmine (29, 30), drug administration was divided into two phases. The first, or dose-response, phase was designed to determine the optimal dose for each patient. In this phase subjects received, under double-blind conditions, placebo or .125 mg, .25 mg, or .50 mg of physostigmine in a random order on separate days. The drug was dissolved in 100 cc of saline and administered at a constant rate for 30 min. In the second, or replication, phase of the study, the dose of

physostigmine previously associated with the best performance on cognitive tests involving storage of information into long-term memory was readministered, as was the placebo infusion. The order of these two infusions was also randomized, and the conditions of administration were double-blind. Two to 4 days generally separated each infusion, which always occurred at the same time of day. A dose of 2.5 mg of propanthine, a cholinergic antagonist that does not cross the blood-brain barrier, was administered intravenously 5 min before the start of every infusion to minimize physostigmine's peripheral effects.

Subjects' memory functioning was assessed by cognitive tasks administered in the following order: 1) Famous Faces Test (32), 2) Digit Span Task, and 3) Recognition Memory Test for either 12 words or 12 pictures (33–35). Approximately 1 week before the administration of physostigmine, baseline cognitive performance was assessed on two occasions. On drug-free days testing began after the infusion started and ended 10 min after the infusion stopped. The more demented subjects were assessed with the picture recognition task and the less demented subjects with the word recognition task. Three trials were completed on the picture or word recognition task. In the first, or study, phase of each trial, patients described each picture briefly or read each word. In the second, or test, phase, the 12 studied items were presented together with 12 similar words or pictures that had not been presented previously. The patient's task was to decide whether each of the 24 items had been presented previously.

These tests were selected to measure the subjects' ability to store information in long-term memory, to be sensitive to an improvement or worsening in performance, to be comprehensible to the subject, and to be completed in the time period of physostigmine's biological activity. The distinction between short-term and long-term memory is an essential feature of many current psychological theories of memory and is supported by studies of patients with hippocampal lesions. Short-term memory is presumed to be of limited capacity and can be measured in seconds. The Digit Span Task is a measure of short-term memory. Long-term memory is essentially of unlimited capacity and is where information is permanently stored. Learning a list of words involves the storage of information in long-term memory. The ability to recall a previously learned name measures retrieval from long-term memory (32–41).

TABLE 1. Recognition Memory in 10 Patients with Alzheimer's Disease During Dose-Response Phase of Physostigmine Treatment

	Mean Percent Correct on the Recognition Memory Test[a]			
		Physostigmine		
Patient	Placebo	.125 mg	.25 mg	.50 mg
1	75.0	60.4	76.4	87.5[b]
2	73.6	70.8	70.8	79.2[b]
3	61.1	66.7	70.8[b]	65.3
4	45.8	69.5[b]	62.5	55.6
5	59.7	81.9[b]	65.3	69.4
6	75.0	79.2	90.3[b]	88.9
7	84.7	80.6	86.1	88.9[b]
8	55.3	66.7[b]	63.9	61.1
9	80.6	77.8	80.5	87.5[b]
10	69.4	75.0	79.2	58.9[b]

[a]Each percent is the mean for 3 trials. Raw scores can be obtained by multiplying the mean percent of correct responses by 24. The number of errors can be obtained by subtracting the raw scores from 24.
[b]The patient's best response.

TABLE 2. Recognition Memory in 10 Patients with Alzheimer's Disease During Replication Phase of Physostigmine Treatment

	Mean Percent Correct on the Recognition Memory Test		
Patient	Placebo	Physostigmine	Change
1	76.38	79.17	2.79
2	55.54	73.62	18.08
3	63.88	63.88	0.00
4	58.33	68.04	9.71
5	65.29	75.00	9.71
6	83.33	97.21	13.88
7	73.58	91.67	18.09
8	55.54	63.88	8.34
9	80.54	72.21	−8.33
10	72.21	75.00	2.79
Mean	68.47	75.97	7.50

RESULTS

Table 1 presents the results obtained from all 10 patients on the picture or word recognition task during the dose-response phase of the study. All patients had their best performance in ability to store information in long-term memory on some dose of physostigmine rather than on the placebo saline infusion. In all of these patients the best dose of physostigmine varied among .125 mg, .25 mg, and .50 mg. Although it was not possible to completely balance the order of drug doses, an analysis of variance performed on the memory test scores with test days as a repeated measures factor revealed no tendency for scores to change with repeated testing ($F=2.5$, $df=3, 27$, $p>.07$). Factors that might predict the dose of physostigmine most likely to enhance memory were not readily apparent, although the data in table 1 suggest that the best dose decreased as patients' ability to perform the task decreased.

The results of the replication phase of the study are presented in table 2. During this phase only 1 patient's performance was better during the same than during the physostigmine infusion. Another patient had an equivalent performance during both infusions, and 8 patients demonstrated a physostigmine-related improvement in long-term memory storage. A paired t test indicated that this enhancement due to physostigmine was significant ($t=2.84$, $df=9$, $p<.01$, one-tailed). Baseline memory test scores differed by an average of 2%.

Two other statistical analyses were also performed on the data from the replication study. A mixed model analysis of variance was performed with order of drug and placebo administration as a between-subjects factor and with drug conditions (physostigmine versus placebo) and learning trials (1, 2, and 3) as orthogonal within-subjects factors. Of the 2 groups formed by considering order of drug administration, 1 consisted of 6 patients who received placebo first and the other consisted of 4 patients who received physostigmine first. The analysis revealed no effect due to order of drug administration and no significant interactions involving order of drug administration ($p>.10$ in all cases). There was, however, a significant increase in percent of correct responses over trials ($F=6.25$, $df=2, 16$, $p<.01$) and a significantly greater percent of

correct responses in the physostigmine condition ($F=6.92$, $df=1, 8$, $p<.03$). The interaction of trials with drug conditions was not significant ($p>.10$). Since it is possible that these data do not satisfy all of the assumptions required for parametric statistical analysis, the scores presented in table 2 were also analyzed by means of a nonparametric sign test. This test also demonstrated that the enhancement of memory due to physostigmine was statistically significant ($p<.02$, one-tailed).

Analysis of the data from the Digit Span Task, which measures the capacity of short-term memory, and the Famous Faces Test, which measures retrieval from long-term memory, indicated that physostigmine had no effect on performance of these tasks.

Baseline memory test scores obtained on the Recognition Memory Test on two occasions before the dose-response phase differed by 2%.

DISCUSSION

Low doses of intravenous physostigmine transiently improved the ability of patients with Alzheimer's disease to store information into long-term memory, as demonstrated by the Recognition Memory Test. This effect was demonstrated twice—in the dose-response phase of the study and again in the replication phase. This finding is consistent with similar effects of physostigmine and arecoline in young normal subjects (29, 30) and with a preliminary report of the effects of intravenous physostigmine on a small group of patients with Alzheimer's disease (42). Following that last report physostigmine, the muscarinic agonist arecoline, and the longer-acting acetylcholinesterase inhibitor tetra-hydroaminoacridine have been administered to a number of patients with Alzheimer's disease. In every instance in which multiple doses of a cholinomimetic agent were administered to a sample of patients with Alzheimer's disease, there was a beneficial response in a variable subgroup of patients. The ability to encode new information into long-term memory was enhanced in the majority of patients in two studies (43, 44) and to a lesser extent in another study (45). Administration of tetra-hydroaminoacridine produced a general global improvement in 9 of 12 patients but a more modest, although positive, effect in another series of patients (46). Physostigmine markedly enhanced a patient's constructional praxis (47) and diminished intrusion errors (48). There have been two negative reports encompassing very few patients with Alzheimer's disease. One tested the effect of a single dose of pilocarpine in a heterogeneous group of elderly people with dementia including Korsakoff's dementia (49). The other study, which investigated the effects of a single dose of intravenous physostigmine in patients with Alzheimer's disease (50), pointed out that in order to find a positive effect of physostigmine it may be critical that "the dose is titrated individually"; that study did not follow such a procedure.

An inevitable question in any study of cholinomimetic agents in Alzheimer's disease is the clinical significance of the drug's effect. In the present investigation the absolute magnitude of physostigmine's effect can be judged by comparison both with nondemented people and with the baseline variability of patients with Alzheimer's disease on recognition memory tests. Compared with nondemented people, the patients in this study were quite impaired even while receiving physostigmine. Baseline memory test scores differed by an average of 2%, considerably less than the drug's effect. Thus, the acute effect of physostigmine to enhance memory was larger and more consistent than the normal day-to-day fluctuation in memory test performance among these patients, even though they remained quite impaired compared with nondemented people. However, until there is long-term administration of cholinomimetic agents to patients with Alzheimer's disease, it will be impossible to judge their ultimate clinical utility.

In summary, these data support the hypothesis that cholinergic neurons are critically involved in the storage of information in long-term memory. Furthermore, they suggest that the cholinergic deficit found on neuropathological examination contributes to the cognitive changes in patients with Alzheimer's disease and that reversal of that deficit may provide an approach to the treatment of the disorder.

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OFFER OF CONFIDENTIAL ACCESS AND CONFIDENTIALITY AGREEMENT

Pursuant to 35 U.S.C. § 355(j)(2)(B), Purepac Pharmaceutical Co. ("Purepac"), a subsidiary of Alpharma Inc., has provided notice (the "Notice Letter") to the undersigned that it intends to market the drug product, galantamine hydrobromide tablets, 4 mg, 8 mg, and 12 mg, under Abbreviated New Drug Application ("ANDA") number 77-585 before the expiration date of U.S. Patent Nos. 4,663,318, 6,099,363, and 6,358,527 (the "Patents"). Such notice sets forth, among other things, a detailed statement of the factual and legal basis of Purepac's opinion that the claims of the Patents are invalid and/or will not be infringed by the commercial manufacture, use or sale of the proposed drug product. For the sole purpose of allowing the undersigned to determine whether an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) should be brought, Purepac hereby offers to provide confidential access to ANDA No. 77-585, subject to the restrictions set forth herein. By requesting such confidential access and acknowledging this Offer of Confidential Access and Confidentiality Agreement ("Agreement"), the undersigned hereby agrees as follows:

(1) This Agreement shall apply to all information, documents and things relating to ANDA No. 77-585 made available or otherwise disclosed by Purepac or its counsel to the undersigned or its counsel in connection with the Notice Letter. Such information and materials are hereinafter collectively referred to as "Confidential Information."

(2) Any copy, summary, extract, description or other document containing Confidential Information shall be subject to the terms of this Agreement to the same extent as the information or document from which such copy, summary, extract, description or other document was made.

(3) Access to Confidential Information shall be limited solely to:

(a) partners and associate attorneys and secretarial, paralegal and staff personnel of outside attorneys for the undersigned;

(b) a single in-house attorney of the undersigned, provided that such in-house attorney (i) makes no further disclosure of all or part of the Confidential Information, (ii) is specifically identified in writing prior to such disclosure and (iii) executes an acknowledgement of the Agreement in the form attached hereto as Exhibit A; and

(c) any outside copying service, provided that before any such disclosure is made the authorized representative of said copying service executes an acknowledgement of the Agreement in the form attached hereto as Exhibit A.

(4) No person to whom any Confidential Information is disclosed shall make any further disclosure thereof.

(5) No person to whom any Confidential Information is disclosed shall use such information except for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the Notice Letter.

(6) Nothing contained herein shall be construed to restrict disclosure and use of documents, information or things to any person who in the course of his business duties had previously prepared, lawfully received or had rightful access to such documents, information or things.

(7) Nothing contained herein shall obligate Purepac to disclose any information to the undersigned relating to ANDA No. 77-585 or any other subject matter whatsoever.

(8) Unless otherwise agreed in writing, Confidential Information, all copies thereof, and any extracts, descriptions or summaries thereof, are to be destroyed or returned to Purepac immediately following the passage of 45 days after the undersigned's receipt of the Notice Letter.

(9) Nothing herein shall prevent disclosure beyond the terms of this Agreement if Purepac agrees to such disclosure in writing or as required by law, in which case the undersigned shall provide Purepac with prior notice sufficient to seek a protective order.

(10) Purepac shall not be deemed to have waived the attorney/client privilege or attorney work product privilege by virtue of this Agreement or the disclosure of any Confidential Information hereunder.

(11) This Agreement shall be governed and construed in accordance with the laws of the State of New York without regard to its conflicts-of-law rules.

ACCORDINGLY, intending to be bound by the terms of this Agreement and agreeing that it is in its respective commercial interest to be so bound, the undersigned does hereby acknowledge its agreement by its signature below.

Dated: _____ Company: _____

By: _____

Name: _____

Its: _____

EXHIBIT A

AGREEMENT CONCERNING MATERIAL
COVERED BY A CONFIDENTIALITY AGREEMENT

The undersigned hereby acknowledges that he or she has received and read the Offer of Confidential Access and Confidentiality Agreement (the "Agreement") executed by _____ on _____. The undersigned agrees to be bound by such terms, and agrees to submit to the jurisdiction of the United States District Court for the Southern District of New York for the purpose of enforcing the terms of the Agreement.

Dated: _____

_____
(Signature)

CERTIFICATE OF SERVICE

I hereby certify that on the 21st day of February, 2006, the attached **NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6) TO PUREPAC PHARMACEUTICAL CO. AND ALPHARMA, INC.** was served upon the below-named counsel of record at the address and in the manner indicated:

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